VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Guidance for Industry

EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR FELINE VICH GL20

FINAL GUIDANCE

This final guidance is intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 00D-1629.

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EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR FELINE

Recommended for Implementation
on June 2001
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND WAS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

EFFECTIVENESS OF ANTHELMINTICS: SPECIFIC RECOMMENDATIONS FOR FELINE

Endorsed by the VICH Steering Committee at Step 7 of the VICH process at its meeting from June 2001

This guidance represents the agency's current thinking on the subject matter and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

Introduction

The present guidance for feline was developed by the Working Group that was established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidances. It should be read in conjunction with the "VICH Effectiveness of Anthelmintics: General Recommendations (EAGR)" which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to the EAGR guidance with the aim of simplicity for readers comparing both documents.

The guidance for feline is part of the EAGR and the aim is: (1) to be more detailed for certain specific issues for feline not discussed in the EAGR; (2) to highlight differences with the EAGR on data recommendations, and (3) to give explanations for disparities with the EAGR guidance.

It is important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend that the sponsors refer to the pertinent procedures described in detail in other published documents e.g., WAAVP Guidelines for Evaluating the Efficacy of Anthelmintics for Dogs and Cats, Veterinary Parasitology ***52***: 179-202, 1994.

A. General Elements

1- The Evaluation of Effectiveness Data

The evaluation of effectiveness data is based on parasite counts (adults, larvae) in dose determination and dose confirmation studies; egg counts/larval identification should be the preferred method to evaluate the effectiveness in field studies.

The controlled test is the most widely accepted of the testing procedures for the evaluation of anthelmintic drug effectiveness. However, the critical test may be appropriate for some intestinal species of parasites, e.g., ascarids.

Adequate parasite infection should be defined in the protocol according to regional prevalence or historic and/or statistical data.

2 - Use of Natural or Induced Infections

Dose determination studies should be conducted using induced infections with either laboratory or recent field isolates.

Dose confirmation studies should be conducted using naturally or artificially infected animals. Generally, when induced infections are used, at least one study should be conducted in naturally infected animals for each parasite claimed on the labelling. *Echinococcus multilocularis* and *Dirofilaria* spp. testing may be conducted using animals harbouring induced infections due to public health considerations for echinococcosis and the complexity of the claims for heartworm. Due to the zoonotic potential of *E. multilocularis* trials conducted using this parasite should be carried out under high biosecurity provisions.

For the following helminths, induced infections may also be the only method to determine effectiveness of the product because of the difficulties in obtaining a sufficient number of infected animals: *Capillaria aerophila, Physaloptera* spp., *Crenosoma vulpis.* For claims against larval stages, only studies with induced infections should be used.

The history of the parasites used in the induced infection studies should be included in the final report.

3 - Number of Infective Parasitic Forms Recommended for Induced Infections

The number to be used is approximate and will depend on the isolate that is used. The final number of larvae used in the infection should be included in the final report. Table 1 shows the range of numbers recommended for common helminths.

Table 1. Range of infective stages recommended to produce adequate infections in feline for anthelmintic evaluation.

Parasites	Range
Small Intestine:	
Toxocara cati	100 - 500
Toxascaris leonina	200 - 3,000
Ancylostoma tubaeforme	100 - 300
Ancylostoma braziliense	100 – 300
Strongyloides stercoralis	1,000 – 5,000
Taenia taeniaeformis	5 – 15
Large Intestine	
Trichuris campanula	100 - 500
Heart	
Dirofilaria immitis	30 – 100*

* For adulticidal or microfilaricidal testing 5 to 15 pairs of adult worms can be transplanted.

4 - Recommendations for the Calculation of Effectiveness

4.1 Criteria to grant a claim

To be granted a claim the following pivotal data should be included:

a) Two dose confirmation studies conducted with a minimum of six adequately infected non-medicated animals (control group) and six adequately infected medicated animals (treated group);

b) The differences in parasite counts between treated and control should be statistically significant ($p<0.05$);

c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data. For some parasites with public health or animal welfare/clinical implications e.g., *E. multilocularis* and *D. immitis*, respectively, higher effectiveness standards (i.e., up to 100%) may be appropriate. The regulatory authority of the region in which the product is intended to be registered should be consulted;

d) The infection of the animals in the study may be deemed adequate based on historical, parasitological and/or statistical criteria;

e) Effectiveness against helminths should be evaluated by examining for the presence or absence of parasitic elements in faecal material or blood. An *E. multilocularis* claim does not need field studies due to public health concerns.

4.2 Number of Animals (Dose Determination and Dose Confirmation Trials)

The minimum number of animals used per experimental group is a critical point. Although the number of animals will depend on the ability to process the data statistically according to the adequate statistical analysis it has been recommended, to achieve harmonization, that the inclusion of at least six animals in each experimental group is a minimum.

In cases where there are several studies none of which have six adequately infected animals in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 animals in the studies and statistical significance could be calculated.

If the differences are significant ($p<0.05$), effectiveness may be calculated and if the infection is deemed adequate, the claim may be granted. Sampling techniques and estimation of worm burden should be similar among laboratories involved in the studies to allow adequate and meaningful extrapolation of the results to the population.

4.3 Adequacy of Infection

With respect to the minimum adequate number of helminths, the decision should be made when the final report is submitted based on historical data, literature review, or expert testimony. Generally, the minimal number of nematodes in feline considered to be adequate is in the range of 5 to 20. Higher counts are to be expected with *A. tubaeforme*.

4.4 Label Claims

A claim for effectiveness against life stages of each parasite should refer to each stage in the case of natural infections, or age in days in the case of induced infection. Table 2 is provided as a guide for the recommended time of treatment of induced infections.

Table 2. Recommended time of treatment after infection

Parasite	Adult Stages	Larval Stages
S. stercoralis	5 to 9 days	
T. campanula	84 days	
A. tubaeforme	> 21 days	6 to 8 days (L4)
A. braziliense	> 21 days	6 to 8 days (L4)
T. cati	60 days	3 to 5 days (L3/L4) 28 days (L4/L5)
T. leonina	70 days	35 days (L4)
D. immitis	180 days	2 days (L3), 20 to 40 days (L4) 70 to 120 days (L5), 220 days (microfilariae)
T. taeniaeformis	> 35 days	

With the majority of parasites approximately seven days is a sufficient time period from the termination of treatment until the test animals are necropsied. The following parasites are the exception to the above general recommendation:

Physaloptera spp., *C. aerophila, E. multilocularis, T. taeniaeformis, Dipylidium caninum*: 10 to 14 days;
C. vulpis: 14 days;
D. immitis: varies by trial design.

For claims against transmammary transmission of *T. cati* somatic larvae of natural or artificially infected pregnant queens should be treated prior to or just after parturition and the effectiveness checked by counting the larvae in the queen milk and/or the adult worms in the small intestines of the litter.

5 - Treatment Procedures

The method of administration (oral, parenteral, and topical) and extent of activity of the product will influence the protocol design. It is advisable to consider the weather and animal relationship and bathing with regard to effectiveness of topical formulations.

For oral formulations, palatability studies should always be included in the evaluation of the effectiveness of the product. For products administered topically, the impact of weather (e.g., rainfall, UV light), bathing and coat length should be included in the evaluation of the effectiveness of the product.

6 - Animal Selection, Allocation and Handling

Approximately six-month-old feline are generally suitable for controlled studies, however, older and younger animals can also be used and the following exceptions should be taken into account:

- *S. stercoralis*: less than six months;
- *A. braziliense, A. tubaeforme six* to 16 weeks;
- *T. cati, T. leonina:* four to 16 weeks;
- *D. caninum:* three months or older.

Naturally infected animals should be selected based on egg output or expelled proglottids in gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. They should be assigned to each group and replicated using an adequate method that should be described in the final report. Replications should cover each factor that may have an impact on the final evaluation of the effectiveness of the formulation. Animal housing, feeding and care should follow recommendations for welfare for felines. Animals should be acclimatized for at least seven days to the experimental facilities and personnel. Animals should be monitored daily to determine adverse reactions.

B. Specific evaluation studies

1- Dose determination studies

No species specific recommendations.

2- Dose confirmation studies

No species specific recommendations.

3 - Field Effectiveness studies

Field (clinical) studies should not be conducted with feline infected with *E. multilocularis* and *D. immitis.*

4 - Persistency Effectiveness studies

Due to the differing biology of helminths in feline and the lack of experience with persistent effectiveness for these parasites, no recommendations can be provided.